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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Rajiv Yadav
McCutchen, Doyle, Brown & Enersen, LLP
28th Floor
Three Embarcadero Center
San Francisco, CA 94111

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,764	LENZ ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner reviewing your application has changed. The new examiner is Jehanne Sitton. To aid in properly correlating the papers for the instant application, please indicate examiner Jehanne Sitton in future correspondence with regard to the instant application.

2. Currently, claims 47-60 are pending in the instant application. The amendments and arguments have been thoroughly reviewed but were insufficient to place the instant application in condition for allowance. The following rejections are newly applied. They constitute the complete set presently applied to the instant application. Response to applicant's arguments follows, where appropriate. This action is NON-FINAL.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

4. The rejections under 35 USC 112/2nd paragraph made in the previous office action are withdrawn in view of the amendments to the claims.

5. The rejections of claims 47-49 under 35 USC 102(b) and claims 50-60 under 35 USC 103(a) made in the previous office action are withdrawn in view of the new grounds of rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claims 58-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 58-60 are indefinite because it is unclear if the kit of claim 58 contains any components. The word 'comprise' has been deleted from line 2 of the claim and thus it is unclear if the recitation of "positive controls, negative controls..." are components of the kit.

Claim Rejections - 35 USC § 102

7. Claim 47 is rejected under 35 USC 102(b) as being anticipated by Wilson et al (hereinafter referred to as Wilson; Blood, vol. 89, pages 601-609, 1997).

Wilson teaches a method for screening cancer cells for sensitivity to a chemotherapeutic drug. The method of Wilson involves taking a biological sample of cancer cells from a patient, in the case of Wilson, the cancer cells are from tumor samples of patients with Non-Hodgkins Lymphoma (see page 602, col. 1 "Patients and Staging"). Wilson teaches that the genotype (identification of mutation by DGGE and sequencing, page 603, col. 1) was determined for a pre-selected gene, in the case of Wilson, this was p53 (see abstract and page 603, col. 1). Wilson teaches that p53 overexpression was determined for tumor cells that exhibited p53 mutations, and found that 13 of 16 tumors with mutations showed p53 overexpression (table 2, and page 603, col. 2, last para). In the last paragraph of column 2 on page 63, Wilson teaches that there was a very good concordance between overexpression and mutation for p53 ("wherein

said genotype determines the intratumoral expression of said gene"). Wilson further teaches determining the sensitivity of tumors, which contained a good concordance between mutation and overexpression (see table 1, and page 604, col. 2, 1st full para), to chemotherapy. Wilson teaches that tumors with p53 abnormality (13 of 16 contained concordance between mutation and overexpression) were significantly more likely to be drug resistant to EPOCH (infusional etoposide, vincristine and doxorubicin, and bolus prednisone and cyclophosphamide) chemotherapy by both univariate and multivariate analysis (see page 604, col. 2, last para; and page 607, col. 2, first full para). Further, Wilson teaches that because p53 status will likely become and important clinical parameter, the specificity and sensitivity of p53 immunochemistry was determined and found to be a reliable method of determining p53 status. As p53 mutation status was found to be a statistically significant indicator of sensitivity to EPOCH, Wilson inherently teaches correlating p53 expression to sensitivity to EPOCH.

8. Claim 47 is rejected under 35 U.S.C. 102(b) as being anticipated by Tamiya et al (hereinafter referred to as Tamiya; Blood, vol. 91, pages 3935-3942; May 15, 1998).

Tamiya teaches detecting two mutations in the FAS gene (pre selected gene) each mutation occurring on one transcript. The first mutation, a 5 bp deletion and a 1bp insertion in exon 2, and the 2nd, a lack of exon 4, caused premature termination of both alleles and resulted in the loss of expression of surface FAS antigen on adult T-cell leukemia cells (ATL) (see abstract). Tamiya teaches that samples were from PBMCs or lymph node cells (see sentence bridging pages 3935-3936; "taking a biological sample of cancer cells from a patient"). The mutations taught by Tamiya (genotype) correlated to the intratumoral expression of the gene (see abstract).

Further, Tamiya teaches that ATL samples that lacked expression of FAS antigen were resistant to anticancer drugs in vivo "correlating said gene expression to said sensitivity to said chemotherapeutic drug". Therefore, Tamiya inherently teaches a method of screening cancer cells for sensitivity to a chemotherapeutic drug and correlates gene expression of a preselected gene (Fas antigen) to sensitivity to a chemotherapeutic drug and anticipates the instantly claimed invention.

9. Claims 57-59 are rejected under 35 USC 102(b) as being anticipated by New England Biolabs catalog (1996, page 102).

New England Biolabs teaches a kit which contains a DNA ladder X174 DNA-Hae III Digest which contains base pairs on the order of 1,353 base pairs to 72 base pairs. Alternatively, New England Biolabs teaches a kit which contains a DNA ladder pBR322 DNA-BstN I Digest which contains base pairs on the order of 1, 857 to 13 base pairs (see page 102). Either of these DNA ladders could be used as sequencing markers and appear to be a component of the kit of claim 58. Additionally, the DNA ladder is provided in a solution of 10 mM Tris and 1mM EDTA (claim 59). It is noted that the use for the kit and the instructions for the kit carry no patentable weight as they merely set forth an intended use for the components of the kit. Additionally, the components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product..."

Claim Rejections - 35 USC § 103

10. Claims 48-56 are rejected under 35 USC 103(a) as being unpatentable over the combination of Horie et al (hereinafter referred to as Horie; Cell Structure and Function, vol. 20, pages 191-197; 1995) and Leichman et al (hereinafter referred to as Leichman; Journal of Clinical Oncology; vol. 15, pages 3223-3229; 1997) in view of Ruano et al (hereinafter referred to as Ruano; US Patent 5,972,614), and further in view of, in the alternative, Wilson, or Tamiya.

Horie teaches that triple tandemly repeated sequences are known to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals (see abstract, and page 191, 2nd column). Horie teaches that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat (see abstract). While Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility (see page 195 column 2, to page 196, column 1, 2nd para). Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs, however, Leichman et al disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil, 5-FU) by taking a biological sample (colorectal cancer biopsy) of a subject and determining the intratumoral expression of the TS gene (see page 3224, page 3226 last para). Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU. Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of

therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Wilson teaches a method of screening cancer cells for sensitivity to chemotherapeutic drugs by taking a biological sample of cancer cells and determining the genotype of p53 (a preselected gene). Wilson teaches that the presence of mutated p53 was correlated to p53 expression and that tumors with mutated p53 and exhibited p53 overexpression were significantly more resistant to treatment with EPOCH. Wilson also teaches that identification of molecular or biological markers of drug resistance may allow for the development of a prognostic index.

Tamiya teaches a method of screening cancer cells for sensitivity to chemotherapeutic drugs by taking a biological sample of cancer cells by detecting mutations in Fas antigen. The mutations taught by Tamiya (genotype) correlated to the intratumoral expression of the gene (see abstract). Further, Tamiya teaches that adult T cell leukemia samples that lacked expression of FAS antigen were resistant to anticancer drugs in vivo.

Ruano teaches that genetic variability is a determinant of a patient's response to therapy. Ruano teaches that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is possible to create a prognostic test for customizing therapy based on a patients genotype (see column 7, lines 3-15). Further, Ruano teaches that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences (see col. 12, lines 40-42).

Although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening colorectal cancer cells for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for chemosensitivity of tumors to chemotherapy drugs. The ordinary artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer could be customized for patients according to the number of TS repeats that tumor cells possessed because Ruano teaches that it is possible to create a prognostic test for customizing therapy based on a patients genotype and Wilson teaches that identification of molecular or biological markers of drug resistance may allow for the development of a prognostic index. Further, Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare toxicity to patients unlikely to respond and would allow faster progress in new drug development. Both Wilson and Tamiya provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected wherein the genotype determines the intratumoral expression of the gene and correlating expression to sensitivity to the chemotherapeutic drug. Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences was found to

be polymorphic among individuals (see abstract, and page 191, 2nd column) and 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for sensitivity to 5-FU in colorectal cancer cells by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene for the purpose of determining if a genotypic assay could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer. As Horie teaches that the number of repeats is associated with TS expression, the teachings of Horie provide a reasonable expectation of success to screen cancer cells for sensitivity to chemotherapy drugs by determining the genotype (number of repeats in each allele) of TS wherein the genotype determines the intratumoral expression of TS and correlating gene expression to sensitivity to a chemotherapeutic drug.

11. Claims 57-60 are rejected under 35 USC 103(a) as being unpatentable over of Horie and Leichman in view of Ruano, and further in view of Wilson or Tamiya as applied to claims 48-56 above, and further in view of Erlich (US Patent 5,468,613) and New England biolabs.

The teachings of Horie and Leichman in view of Ruano, and further in view of Wilson or Tamiya are set forth above. Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya do not teach a kit comprising DNA tandemly repeated sequence of the TS gene, however Erlich teaches constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays (see abstract, col. 5, lines 32-40). Further, Erlich teaches providing kits which include such sequence specific oligonucleotides. Therefore, it would have

been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct sequence specific oligonucleotides as taught by Erlich that contained tandemly repeated sequences of the TS gene for use in the method of Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya for the purpose of providing a sequence specific oligonucleotide that could be used to determine a tumor cell's TS genotype in the screening method of Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya. The ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of provided pre-weighed, premeasured reagents that would make the method of Horie & Leichman, in view of Ruano, and further in view of Wilson or Tamiya more convenient to perform. It would have been further obvious to provide the oligonucleotides in a solution of TE buffer as such was commonly used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog. It is noted that he use for the kit and the instructions in the kit carry no patentable weight. It is further noted that the temperature of the buffer solution carries no patentable weight as it does not provide any structural limitation to the kit.

Response to Arguments

12. Applicant's traverse the rejections in the previous office action. The response asserts that Leichman does not teach that an altered phenotype is predictive of gene expression. This argument was thoroughly reviewed but were found unpersuasive as the claims do not require a correlation between an altered phenotype and gene expression. The response further asserts that the office has failed to consider the 'teaching away' in Horie, that TS overexpression can be regulated at the translational as well as the transcriptional level. This argument has been

thoroughly reviewed but was found unpersuasive. Firstly, Horie teaches possible mechanisms for the enhancing effect of the unique repeated structure and teaches that TS overexpression could be regulated either at a transcriptional level or a post-transcriptional level. However, Horie teaches that either possibility involves the unique repeated structure playing a role (see pages 195, col. 2-196, col. 1, first full para). Therefore, Horie provides a reasonable expectation of success that the expression of TS is also regulated by the repeat structure. Secondly, it is noted that the instant claims are to a screening method. The teachings of Horie and Leichman, in view of the large amount of literature available in the art at the time of the instant invention, with regard to motivation to screen for cancer cells which are sensitive to chemotherapeutic drugs due to aberrant genotypes, gene expression, or both, provide the ordinary artisan with motivation to screen colorectal cancer cells for differences in number of repeats in the TS gene and to determine if such is associated with the observation disclosed in Leichman that expression of TS was correlated to chemosensitivity. As Horie teaches that the number of repeats is associated with TS expression, the teachings of Horie provide a reasonable expectation of success to screen cancer cells for sensitivity to chemotherapy drugs by determining the genotype (number of repeats in each allele) of TS wherein the genotype determines the intratumoral expression of TS and correlating gene expression to sensitivity to a chemotherapeutic drug.

Conclusion

13. No claims are allowable over the cited prior art.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Jehanne Sitton
Primary Examiner
Art Unit 1634
5/24/04